

Applicant : Short, et al.  
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Attorney's Docket No.: 564462001824  
D1370-14US  
PATENT

Amendment to the Specification:

Please amend the specification as follows:

**Please replace the first paragraph on page 1 (entitled "CROSS-REFERENCE TO RELATED APPLICATIONS"), which is paragraph [0001], page 1, of U.S. Pat. App. Publication No. 20040091968 ("the '968 publication"), with the following amended paragraph:**

[0001] This application is a continuation-in-part (CIP) of U.S. Patent Application Serial No. (USSN) 09/866,379, filed May 24, 2001, now U.S. Patent No. 6,855,365, issued February 15, 2005 ~~now pending~~, which is a CIP of USSN 09/580,515, filed May 25, 2000, now U.S. Patent No. 6,720,014, issued April 13, 2004 ~~now pending~~, which is a CIP of USSN 09/318,528, filed May 25, 1999, now U.S. Patent No. (USPN) 6,183,740, issued February 6, 2001, which is a CIP of USSN 09/291,931, filed April 13, 1999, now USPN 6,190,897, issued February 20, 2001, which is a continuation of USSN 09/259,214, filed March 1, 1999, now USPN 6,110,719, issued August 29, 2000, which is a divisional of USSN 08/910,798, filed August 13, 1997, now USPN 5,876,997, issued March 2, 1999, all of which are hereby incorporated by reference in their entirety for all purposes.

**Please replace paragraph [0116], of the '968 publication, with the following amended paragraph:**

[0116] A "comparison window", as used herein, includes reference to a segment of any one of the number of contiguous positions selected from the group consisting of from 20 to 600, usually about 50 to about 200, more usually about 100 to about 150 in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. Methods of alignment of sequence for comparison are well-known in the art. Optimal alignment of sequences for comparison can be conducted, e.g., by the local homology algorithm of Smith & Waterman, Adv. Appl. Math. 2:482, 1981, by the homology

alignment algorithm of Needleman & Wunsch, J. Mol. Biol 48:443, 1970, by the search for similarity method of person & Lipman, Proc. Nat'l. Acad. Sci. USA 85:2444, 1988, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, Wis.), or by manual alignment and visual inspection. Other algorithms for determining homology or identity include, for example, in addition to a BLAST program (Basic Local Alignment Search Tool at the National Center for Biological Information), ALIGN, AMAS (Analysis of Multiply Aligned Sequences), AMPS (Protein Multiple Sequence Alignment), ASSET (Aligned Segment Statistical Evaluation Tool), BANDS, BESTSCOR, BIOSCAN (Biological Sequence Comparative Analysis Node), BLIMPS (BLocks IMProved Searcher), FASTA, Intervals & Points, BMB, CLUSTAL V, CLUSTAL W, CONSENSUS, LCONSENSUS, WCONSENSUS, Smith-Waterman algorithm, DARWIN, Las Vegas algorithm, FNAT (Forced Nucleotide Alignment Tool), Framealign, Framesearch, DYNAMIC, FILTER, FSAP (Fristensky Sequence Analysis Package), GAP (Global Alignment Program), GENAL, GIBBS, GenQuest, ISSC (Sensitive Sequence Comparison), LALIGN (Local Sequence Alignment), LCP (Local Content Program), MACAW (Multiple Alignment Construction & Analysis Workbench), MAP (Multiple Alignment Program), MBLKP, MBLKN, PIMA (Pattern-Induced Multi-sequence Alignment), SAGA (Sequence Alignment by Genetic Algorithm) and WHAT-IF. Such alignment programs can also be used to screen genome databases to identify polynucleotide sequences having substantially identical sequences. A number of genome databases are available, for example, a substantial portion of the human genome is available as part of the Human Genome Sequencing Project (J. Roach, [http://weber.u.Washingt-on.edu/about.roach/human\\_genome\\_progress-2.html](http://weber.u.Washingt-on.edu/about.roach/human_genome_progress-2.html)) (Gibbs, 1995). At least twenty-one other genomes have already been sequenced, including, for example, *M. genitalium* (Fraser et al., 1995), *M. jannaschii* (Bult et al., 1996), *H. influenzae* (Fleischmann et al., 1995), *E. coli* (Blattner et al., 1997), and yeast (*S. cerevisiae*) (Mewes et al., 1997), and *D. melanogaster* (Adams et al., 2000). Significant progress has also been made in sequencing the genomes of model organism, such as mouse, *C. elegans*, and *Arabidopsis* sp. Several databases

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containing genomic information annotated with some functional information are maintained by different organization, and are accessible via the internet.

**Please replace paragraph [0211], of the '968 publication, with the following amended paragraph:**

[0211] The invention also provides for the use of proprietary codon primers (containing a degenerate N,N,N sequence) to introduce point mutations into a polynucleotide, so as to generate a set of progeny polypeptides in which a full range of single amino acid substitutions is represented at each amino acid position (gene site saturation ~~-saturated~~-mutagenesis (GSSM)). The oligos used are comprised contiguously of a first homologous sequence, a degenerate N,N,N sequence, and preferably but not necessarily a second homologous sequence. The downstream progeny translational products from the use of such oligos include all possible amino acid changes at each amino acid site along the polypeptide, because the degeneracy of the N,N,N sequence includes codons for all 20 amino acids.